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Concise synthesis of (+)-conduritol F and inositol analogues from naturally available (+)-*proto*-quercitol and their glucosidase inhibitory activity

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ABSTRACT

An effective synthesis of (+)-conduritol F, (+)-*chiro*- and (+)-*epi*-inositols from naturally available (+)-*proto*-quercitol is described. This synthetic method provides a concise synthesis of cyclitols in enantiomerically pure form. Of the synthesized cyclitols, (+)-conduritol F potently inhibits type I α-glucosidase with an IC_{50} value of 86.1 μM, which is five times greater than the standard antidiabetic drug, acarbose.

Conduritols are cyclitol derivatives possessing four contiguous hydroxyl groups on cyclohexene ring. There are ten possible stereoisomers; four enantiomeric pairs (conduritols B, C, E and F) and two *meso*-forms (conduritols A and D) (Fig. 1). Interest in conduritols and their analogues have been amplified due to synthetic challenge and presence of a variety of biological activities such as antifeedant, antibiotics, antileukemics and growth-regulation.[1] Currently, as a vital motif in potent anticancer narciclasine[2] and antidiabetic conduritol A,[3] facile and efficient synthetic approaches have been developed to produce optically pure conduritols in large quantity.

Over the course of our current research on new chemical entities as glycosidase inhibitors,[4] we recently reported the synthesis and inhibitory activity of amino quercitols from naturally available (+)-*proto*-quercitol.[4b] Although the starting quercitol has five contiguous hydroxyl groups on cyclohexane ring, exclusive formation of single bis-acetonide is crucial to obtain optically pure amino quercitols in few steps. With the success of our approach in hand, we expand the application to the synthesis other cyclitols.

Conduritol F is our first target because of prominent bioactivities and low natural abundance. Regardless of the presence of an unsaturation in conduritol F and one additional hydroxyl group in (+)-*proto*-quercitol, their gross structure and relative configuration are identical. Thus, dehydration of starting material would readily generate the desired product. Although several conduritols, including conduritol F, have been principally prepared through microbial and photo-oxidations of halogenated benzene,[2,5] vicinal-diols obtained after oxidation inevitably existed as a mixture of two or more stereoisomers. Therefore, preparation of conduritol F from optically pure starting materials is likely to be a method of choice to circumvent such problems. However, these approaches were limited by low yield of conduritol F obtained.[6] In this Letter, we report a short and effective synthesis of (+)-conduritol F and its inhibitory activity against types I and IIα-glucosidase. In addition,

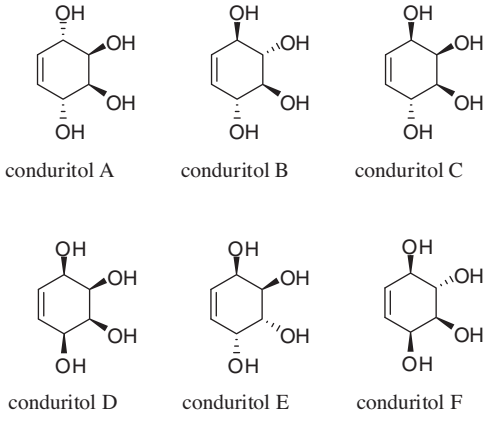

Figure 1. Structures of conduritols.

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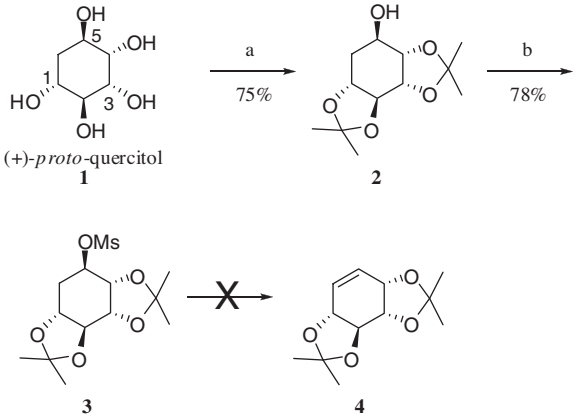
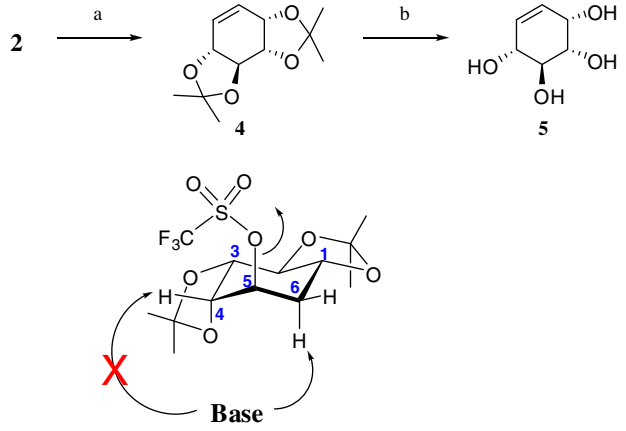


Scheme 1. Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH, DMF, 75%; (b) $MeSO_2Cl$, Et_3N, DMAP, 78%.



Scheme 2. Reagents and conditions: (a) Tf_2O, pyridine, −10 °C, 12 h, 68%; (b) 1.25MHCl/MeOH, rt, 4 h, quant.

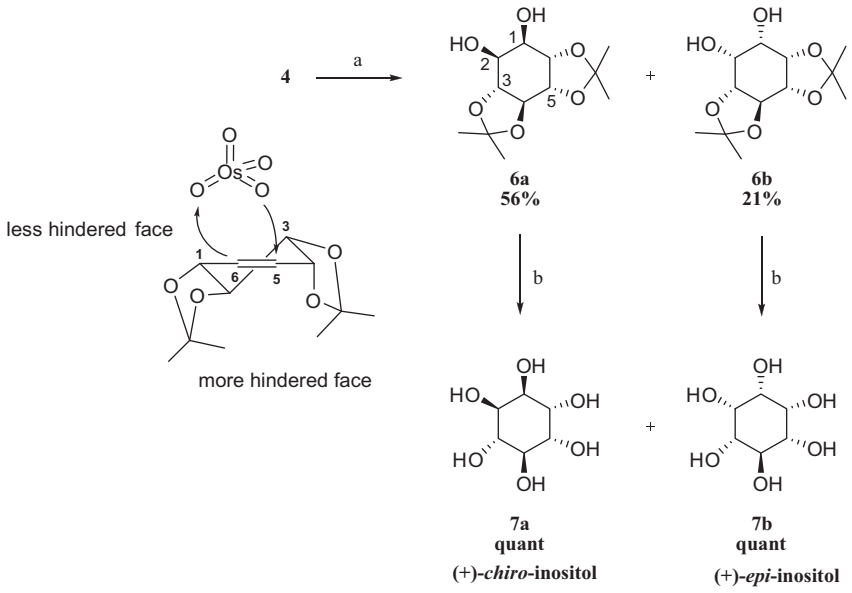
the synthesis process also allowed us to prepare two corresponding inositols, (+)-*epi*- and (+)-*chiro*-isomers.

Our first attempt to synthesize conduritol F from the naturally available (+)-*proto*-quercitol was depicted in Scheme 1. The starting material utilized in this work was facilely isolated from the stems of *Arfeuillea arborescens* using method developed in our laboratory.[7] Notably, this method provides an efficient process, yielding a multiple gram of enantiomerically pure **1** (0.3% yield). It is also environmentally friendly as water is used during extraction and isolation. With compound **1** in hand, the bis-diol moiety was then preferentially protected as the corresponding acetonide to provide the desired compound **2** in an excellent yield. Since one hydroxyl group remains unprotected, it was thus activated with mesyl chloride to afford mesylate ester **3** in 78% yield. Unfortunately, elimination of **3** using various bases such as DBU, pyridine, and *t*-BuOK, in the hope that it would be converted to the protected conduritol **4**, was unsuccessful. More than 80% of **3** was recovered along with **4** in less than 5%. We hypothesized that mesyl group may not be a good leaving group under these conditions.

Having fail elimination reaction of **3** under basic conditions, we turned our focus on olefin formation directly via bis-acetonide **2** using strong dehydrating agents such as thionyl chloride, phosphorusoxychloride, Martin's reagent and trifluoromethanesulfonic anhydride. Treatment of **2** with $SOCl_2$ or $POCl_3$ in pyridine generated the complex mixtures along with trace amount of the desired alkene **4**. Moreover, Martin's sulfurane dehydrating agent was also employed in dry toluene under reflux but inseparable mixture along with 50% starting material were recovered. Fortunately, dehydration of **2** took place smoothly upon addition of Tf_2O in pyridine at −10 °C, affording the protected conduritol F (**4**) as the sole product (Scheme 2). This alternative route not only provided us a short-step conversion of (+)-*proto*-quercitol to conduritol F but also generated the desired product without any congeners.

The specificity of this elimination step is possibly attributed to steric effect. The bulky acetonide may block the proton abstraction at C-4 whereas *trans*-diaxial orientation of H-6_{ax} and the leaving group trifluoromethanesulfonyl facilitates E2 pathway, hence generating protected alkene **4**. Eventually, conduritol F (**5**) was obtained by deprotection of **4** with methanolic HCl. The NMR data and specific rotation (+79.5, c 1.12, MeOH) of our prepared conduritol F[8] were completely identical to those previously reported,[6a,9] confirming the absolute configuration as (+)-conduritol F.

The success in preparation of optically pure (+)-conduritol F allows us to access other cyclitols. The protected conduritol **4** could serve as a chiral building block for single-step conversion to



Scheme 3. Reagents and conditions: (a) OsO_4, NMO, *t*-BuOH/H_2O (1:1), 0 °C; (b) Amberlyst-15, MeOH/H_2O (7:3).

Table 1
α-Glucosidase inhibitory effect of cyclitols **1**, **5**, **7a** and **7b**

	IC_{50} (μM)		
Cyclitol	Baker's yeast	Maltase[a]	Sucrase[a]
1	NI[b]	NI	NI
5	86.1 ± 0.5	NI	NI
7a	1256.1 ± 1.7	NI	NI
7b	475.7 ± 0.9	NI	NI
Acarbose	403.9 ± 0.4	1.50 ± 0.14	2.38 ± 0.02

[a] α-Glucosidase was obtained from rat small intestine.
[b] NI, no inhibition, inhibitory effect less than 30% at 10 mg/mL.

inositol derivatives. Dihydroxylation of **4** using OsO_4 led to the formation of readily separable 3:1 diastereomeric inositols[10] **6a** and **6b** in 77% yield (Scheme 3). The selective formation of **6a** over **6b** could be rationalized by preferential osmylation on the less hindered face of alkene. Consequently, **6a** and **6b** were deprotected by Amberlyst-15 to quantitatively afford (+)-*chiro*-inositol (**7a**)[11] and (+)-*epi*-inositol (**7b**),[12] respectively.

(+)-Conduritol F (**5**) and inositols (**7a** and **7b**) were evaluated for α-glucosidase inhibitory activity using enzymes from two different sources; baker's yeast (type I) and rat small intestine (type II). They selectively inhibited α-glucosidase from baker's yeast,[13] in which **5** displayed highest inhibition with an IC_{50} value of 86.1 μM (Table 1). A potent inhibitory effect (6–16 times) of **5** over its corresponding diols, (+)-*chiro*-inositol (**7a**) and (+)-*epi*-inositol (**7b**), indicates that a half-chair conformation of cyclohexene moiety is more critical in binding active site of the enzyme than additional dihydroxy groups. This observation was also supported by a very low inhibition of (+)-*proto*-quercitol (**1**), a hydroxylated cyclitol of **5**. However, all cyclitols evaluated did not inhibit maltase and sucrase, type II α-glucosidases from rat small intestine.

In summary, we have simply and efficiently achieved short synthesis steps for (+)-conduritol F and inositols: (+)-*chiro*- and (+)-*epi*-inositols, from naturally available (+)-*proto*-quercitol. A key step involves dehydration of protected (+)-*proto*-quercitol (**2**) after addition of Tf_2O in pyridine, therefore taking a total of three steps to produce optically pure conduritol F in excellent yield. Furthermore, our method also provides rapid access to corresponding dihydroxy analogues, (+)-*chiro*- and (+)-*epi*-inositols. A potent inhibition of conduritol F, selectively against typeI α-glucosidase, over related compounds as well as antidiabetic drug acarbose suggests that its half-chair conformation is critical for its biological activity.

Acknowledgments

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Supplementary data

Supplementary data (full experimental details and characterization data for **2**, **4**, **5**, **6a**, **6b**, **7a** and **7b**) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.007.

References and notes

1. For recent review of conduritols see: Gültekin, M. S.; Çelik, M.; Balci, M. *Curr. Org. Chem.* **2004**, *8*, 1159.
2. Kornienko, A.; Evidente, A. *Chem. Rev.* **1982**, *2008*, 108.
3. Borges de Melo, E.; da Silveira Gomes, A.; Carvalho, I. *Tetrahedron* **2006**, *62*, 10277.
4. (a) Phuwapraisirisan, P.; Puksasook, T.; Jong-aramruang, J.; Kokpol, U. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4956; (b) Wacharasindhu, S.; Worawalai, W.; Rungprom, W.; Phuwapraisirisan, P. *Tetrahedron Lett.* **2009**, *50*, 2189; (c) Phuwapraisirisan, P.; Puksasook, T.; Kokpol, U.; Suwanborirux, K. *Tetrahedron Lett.* **2009**, *50*, 5864.
5. (a) Duchek, J.; Adams, D. R.; Hudlicky, T. *Chem. Rev.* **2011**, *111*, 4223; (b) Klbaş, B.; Balci, M. *Tetrahedron* **2011**, *67*, 2355; (c) Finn, K. J.; Collins, J.; Hudlicky, T. *Tetrahedron* **2006**, *62*, 7471; (d) Ogawa, S.; Uetsuki, S.; Tezuka, Y.; Morikawa, T.; Takahashi, A.; Sato, K. *Bioorg. Med. Chem. Lett.* **1999**, *11*, 1493.
6. (a) Cerè, V.; Mantovani, G.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2000**, *56*, 1225; (b) Chiara, J. L.; Valle, N. *Tetrahedron: Asymmetry* **1995**, *6*, 1895; (c) Akiyama, T.; Shima, H.; Ohnari, M.; Okazaki, T.; Ozaki, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3760; (d) Akiyama, T.; Shima, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 5593.
7. Briefly, ground stems (1 kg) of *A. arborescens* were boiled with water (4 L) for 3 h. The decoction was filtered and partitioned twice with equal volume of CH_2Cl_2. The aqueous layer was loaded onto a column chromatography filled with wet Diaion HP20 (1 kg) and excessively eluted with H_2O (10 L). The combined aqueous elutes were lyophilized to afford white powder (3 g), which was subsequently purified by crystallization using hot MeOH.
8. (+)-Conduritol F (**5**): colorless oil, $[\alpha]_D^{25}$ = +79.5 (*c* 1.12, CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 5.71 (ddd, *J* = 9.9, 4.8, 1.9 Hz, 1H), 5.64 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.09 (t, *J* = 4.4 Hz, 1H), 3.85 (d, *J* = 7.6 Hz, 1H), 3.54 (dd, *J* = 10.4, 7.7 Hz, 1H), 3.35 (dd, *J* = 10.3, 4.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 133.8, 128.0, 74.0, 73.9, 72.7, 68.0.
9. (a) Kwon, Y.-U.; Lee, C.; Chung, S.-K. *J. Org. Chem.* **2002**, *67*, 3327; (b) Heo, J.-N.; Holson, E. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1697.
10. An attempt to address configurations of newly generated dihydroxy groups of **6a** and **6b** by NOESY could not be performed since severely overlapped signals of hydroxylated methine protons. However, significant difference in methyl signals of acetonides was observed; **6b** showed separated four methyl resonances whereas 6a demonstrated only three signals.
11. (+)-*chiro*-Inositol (**7a**): pale yellow oil: $[\alpha]_D^{25}$ = +81.9 (*c* 0.45, H_2O); ^1H NMR (D_2O, 400 MHz) δ 3.81 (br s, 2H), 3.54 (br d, *J* = 7.2 Hz, 2H), 3.37 (br d, *J* = 7.2 Hz, 2H); ^{13}C NMR (D_2O, 100 MHz) δ 72.8, 71.7, 70.5.
12. (+)-*epi*-Inositol (**7b**): white solid: $[\alpha]_D^{25}$ = +36.0 (*c* 0.27, H_2O); ^1H NMR (D_2O, 400 MHz) δ 3.86 (br s, 1H), 3.81 (br s, 1H), 3.53 (br s, 2H), 3.37 (dd, *J* = 7.2, 2.4 Hz, 1H), 3.28 (dd, *J* = 9.6, 2.4 Hz, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 74.5, 72.8, 71.8, 71.7, 70.5.
13. Freeman previously reported inhibitory effect of conduritol F against β-galactosidase with an IC_{50} value of 600 μM; Freeman, S.; Hudlicky, T. *Bioorg. Chem. Med. Lett.* **2004**, *14*, 1209.